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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,176	07/18/2003	Elsa A.J.M. Goulmy	2183-6047US	4726

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/623,176	GOULMY ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the office action mailed April 19, 2006 is hereby withdrawn.

Applicant's response and amendments received August 9, 2006 are acknowledged.
Claims 1-6, 8-48, and 50 have been canceled.
Claim 7 has been amended.
Claims 7 and 49 are pending and under examination as they read on methods of inducing tolerance.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 7 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The disclosure of the instant specification is not sufficient to enable a skilled artisan to practice the claimed invention without conducting an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Regarding in vivo methods which rely on previously undescribed and generally unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24

(CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)." The MPEP also states that physiological activity can be considered inherently unpredictable.

Further, in Rasmuson v. SmithKline Beecham Corp., 75 USPQ2d 1297-1303 (CAFC 2005), the court states "[W]here there is "no indication that one skilled in [the] art would accept without question statements [as to the effects of the claimed drug products] and no evidence has been presented to demonstrate that the claimed products do have those effects," an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement" and "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The instant claims encompass administration of a peptide consisting of SEQ ID NO:2 for the induction of tolerance. The specification does not provide a precise definition for tolerance, but lines 17-20 of page 7 indicate that "The peptides and other molecules according to the invention are useful to induce tolerance of the donor immune system in HA-1 negative donors, so that residual peripheral blood lymphocytes in the eventually transplanted organ or the bone marrow, as it may be do not respond to host HA-1 material in an HA-1 positive recipient. In this way, GvHD will be prevented or

mitigated." The specification teaches that CTL recognizing the peptide consisting of SEQ ID NO:2 in the context of the HLA-A2.1 molecule can be generated in culture, and that cells of similar reactivity can be isolated from post bone marrow transplant leukemia patients (see Example 1). However, the specification does not provide a working example wherein the peptide consisting of SEQ ID NO:2 has been administered in vivo to induce tolerance.

The induction of tolerance has been called the "Holy Grail" of transplantation, and like the grail itself, tolerance induction has remained an elusive goal (Schroeder et al., J. Surg. Res. 2003, 111:109:119, see entire document particularly the abstract and page 117). For example, in type I diabetes Pozzilli et al. demonstrate that while the induction of tolerance would be expected, it simply does not occur (Diabetologia 2000, 43:1000-1004). Other unsuccessful examples of tolerance induction in humans are known in the art. *Marketletter* (9/13/99) teaches the complete failure of tolerance induction in human trials. Both Myloral (for multiple sclerosis) and Colloral (for rheumatoid arthritis) provided successful results in inducing tolerance in animal models, however, both were complete failures in human trials. Further, Goodnow states that "Obtaining the desired response (tolerance) with these strategies (for tolerance induction) is unpredictable because many of these signals (tolerogenic) have both tolerogenic and immunogenic roles" (The Lancet, 2001, 357:2115-2121, see entire document, particularly the abstract). Goodnow goes on to teach that while the induction of oral tolerance might be considered "an attractive notion", the method has failed in humans because of the lack of understanding of the mechanisms involved (page 2120, column 2). Applicant's method of inducing tolerance relies upon the administration of a peptide antigen. Schroeder et al. teach that administration of peptides has not yet been reported to induce tolerance in larger animals and primates (see particularly the paragraph spanning pages 116 and 117). Schroeder et al. further teach that it may not be possible to induce tolerance to donor tissue in a specific fashion such that the ability of the host's immune to respond to other dangers such as infection are unimpaired and that the durability of induced tolerance, the immune requirements to maintain tolerance, and the factors that may break tolerance are all unknown (see particularly the middle of the left

column of page 117). Chronic rejection is the primary reason for the failure of most grafts, yet the pathophisiology of this entity is unknown and the impact of tolerance induction on the genesis of chronic rejection is also unclear (Ibid.). What is clear is that "the human immune system is a remarkably complex and redundant mechanism that may not allow circumventing of such a basic function as recognition of nonself" (Ibid., the right column of page 117).

As discussed above, the specification does not provide a working example wherein tolerance was induced in a patient via applicant's claimed method. Given this lack of guidance and the teachings of the art concerning the multiple failures of inducing tolerance in humans and all of the unknowns involved in this process, a skilled artisan would not accept without question that applicant's method would work, and as such the teachings of the instant disclosure cannot be considered an enabling disclosure of the claimed method. In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir.1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working examples, the unpredictability of the art, and the breadth of the claims, a skilled artisan would be required to perform undue trials and errors to practice the claimed invention.

4. No claims are allowable.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is 571-272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Patent Examiner
Technology Center 1600
August 29, 2006

9/1/06

G.R. EWOLDT, PH.D.
PRIMARY EXAMINER